EXHIBIT I

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT J

PDR® 48 EDITION 1994

PHYSICIANS' DESK REFERENCE®

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Marion Merrell Dow—Cont.

lized as needed, whereas in the second study antacid tablets were used.

Maintenance Therapy After Healing of Duodenal Ulcer

Two double-blind randomized placebo-controlled U.S. multicenter trials have demonstrated that sucralfate (1 gm bid) is effective as maintenance therapy following healing of duodenal ulcers.

In one study, endoscopies were performed monthly for 4 months. Of the 254 patients who enrolled, 239 were analyzed in the intention-to-treat life table analysis presented below.

Duodenal Ulcer Recurrence Rate (%)

		Months of Therapy			
Drug	N	1	2	3	4
CARAFATE	122	20*	30*	38**	42**
Placebo	117	33	46	55	63

*p < 0.05, **p < 0.01

Prn antacids were not permitted in this study.

In the other study, scheduled endoscopies were performed at 6 and 12 months, but for cause endoscopies were permitted as symptoms dictated. Median symptom scores between the sucralfate and placebo groups were not significantly different. A life table intention-to-treat analysis for the 94 patients enrolled in the trial had the following results:

Duodenal Ulcer Recurrence Rate (%)

Drug	N	6 months	12 months
CARAFATE	48	19*	27*
Placebo	46	54	65

*p < 0.002

Prn antacids were permitted in this study.

Data from placebo-controlled studies longer than 1 year are not available.

INDICATIONS AND USAGE

CARAFATE® (sucralfate) is indicated in:

- Short-term treatment (up to 8 weeks) of active duodenal ulcer. While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.
- Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate.

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the posthealing frequency or severity of duodenal ulceration.

Special Populations: Chronic Renal Failure and Dialysis Patients:

When sucralfate is administered orally, small amounts of aluminum are absorbed from the gastrointestinal tract. Concomitant use of sucralfate with other products that contain aluminum, such as aluminum-containing antacids, may increase the total body burden of aluminum. Patients with normal renal function receiving the recommended doses of sucralfate and aluminum-containing products adequately excrete aluminum in the urine. Patients with chronic renal failure or those receiving dialysis have impaired excretion of absorbed aluminum. In addition, aluminum does not cross dialysis membranes because it is bound to albumin and transferrin plasma proteins. Aluminum accumulation and toxicity (aluminum osteodystrophy, osteomalacia, encephalopathy) have been described in patients with renal impairment. Sucralfate should be used with caution in patients with chronic renal failure.

Drug Interactions

Some studies have shown that simultaneous sucralfate administration in healthy volunteers reduced the extent of absorption (bioavailability) of single doses of the following drugs: cimetidine, ciprofloxacin, digoxin, ketoconazole, norfloxacin, phenytoin, ranitidine, tetracycline, and theophylline. Subtherapeutic prothrombin times with concomitant warfarin and sucralfate therapy have been reported in spontaneous and published case reports. However, two clinical studies have demonstrated no change in either serum warfarin concentration or prothrombin time with the addition of sucralfate to chronic warfarin therapy

The mechanism of these interactions appears to be nonsystemic in nature, presumably resulting from sucralfate binding to the concomitant agent in the gastrointestinal tract. In all cases studied to date (cimetidine, ciprofloxacin, digoxin, ranitidine, and warfarin), dosing the concomitant medication 2 hours before sucralfate eliminated the interaction. Because of the potential of CARAFATE to alter the absorption of some drugs, CARAFATE should be administered separately from other drugs when alterations in bioavailability are felt to be critical. In these cases, patients should be monitored appropriately.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy

Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2700 patients treated with sucralfate tablets, adverse effects were reported in 129 (4.7%).

Constipation was the most frequent complaint (2%). Other adverse effects reported in less than 0.5% of the patients are listed below by body system:

Gastrointestinal: diarrhea, nausea, vomiting, gastric discomfort, indigestion, flatulence, dry mouth

Dermatological: pruritus, rash

Nervous System: dizziness, insomnia, sleepiness, vertigo

Other: back pain, headache

Postmarketing reports of hypersensitivity reactions, including urticaria (hives), angioedema, respiratory difficulty, and rhinitis have been received. However, a causal relationship has not been established.

OVERDOSAGE

There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

Active Duodenal Ulcer: The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

Maintenance Therapy: The recommended adult oral dosage is 1 gm twice a day.

HOW SUPPLIED

CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47), 120 (NDC 0088-1712-53), and 500 (NDC 0088-1712-55) and in Unit Dose Identification Paks of 100 (NDC 0088-1712-49). Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 on the other.

Prescribing Information as of October 1992
Marion Merrell Dow Inc.
Kansas City, MO 64114

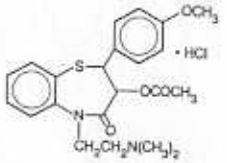
Shown in Product Identification Section, page 316

CARDIZEM® CD Capsules ℞
(diltiazem hydrochloride)
120 mg, 180 mg, 240 mg, and 300 mg

Prescribing information for this product, which appears on pages 1368–1370 of the 1993 PDR, has been completely revised as follows. Please write "See Supplement B" next to the product heading.

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98.

CARDIZEM CD is formulated as a once-a-day extended release capsule containing either 120 mg, 180 mg, 240 mg, or 300 mg diltiazem hydrochloride.

Also contains: black iron oxide, ethylcellulose, FD&C Red #1, fumaric acid, gelatin-NF, sucrose, starch, talc, titanium dioxide, white wax, and other ingredients.

For oral administration.

CLINICAL PHARMACOLOGY

The therapeutic effects of CARDIZEM CD are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action

Hypertension. CARDIZEM CD produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension, thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina. CARDIZEM CD has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work loads. Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by diltiazem. In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects

Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data have no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

In hypertensive patients, CARDIZEM CD produces antihypertensive effects both in the supine and standing positions. In a double-blind, parallel, dose-response study utilizing doses ranging from 90 to 540 mg once daily, CARDIZEM CD lowered supine diastolic blood pressure in an apparent linear manner over the entire dose range studied. The changes in diastolic blood pressure, measured at trough, for placebo, 90 mg, 180 mg, 360 mg, and 540 mg were -2.9, -4.5, -6.1, -9.5, and -10.5 mm Hg, respectively. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects. CARDIZEM CD decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pres-

...ure is usually reduced. Chronic therapy with CARDIZEM CD produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. CARDIZEM CD reduces the renal and peripheral effects of angiotension II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

In a double-blind, parallel dose response study of doses from 90 mg to 480 mg once daily, CARDIZEM CD increased time to termination of exercise in a linear manner over the entire dose range studied. The improvement in time to termination of exercise utilizing a Bruce exercise protocol, measured at trough, for placebo, 60 mg, 120 mg, 240 mg, 360 mg, and 480 mg was 29, 40, 56, 51, 69 and 68 seconds, respectively. As doses of CARDIZEM CD were increased overall angina frequency was decreased. CARDIZEM CD, 180 mg once daily, or placebo was administered in a double-blind study to patients receiving concomitant treatment with long-acting nitrates and/or beta-blockers. A significant increase in time to termination of exercise and a significant decrease in overall angina frequency was observed. In this trial the overall frequency of adverse events in the CARDIZEM CD treatment group was the same as the placebo group.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM to patients in doses of up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation. (See WARNINGS.)

Pharmacokinetics and Metabolism

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. CARDIZEM undergoes extensive metabolism in which only 2% to 4% of the unchanged drug appears in the urine.

Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2 to 5 hours for diltiazem.

In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive in vitro ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma diltiazem concentrations appear to be in the range of 50 to 200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

CARDIZEM CD Capsules. When compared to a regimen of CARDIZEM tablets at steady-state, more than 95% of drug is absorbed from the CARDIZEM CD formulation. A single 360-mg dose of the capsule results in detectable plasma levels within 2 hours and peak plasma levels between 10 and 14 hours; absorption occurs throughout the dosing interval. When CARDIZEM CD was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected. Dose-dumping does not occur. The apparent elimination half-life after single or multiple dosing is 5 to 8 hours. A departure from linearity similar to that seen with CARDIZEM tabets and CARDIZEM SR capsules is observed. As the dose of CARDIZEM CD capsules is increased from a daily dose of 120 mg to 240 mg, there is an increase in the area-under-the-curve of 2.7 times. When the dose is increased from 240 mg to 360 mg there is an increase in the area-under-the-curve of 1.6 times.

INDICATIONS AND USAGE

CARDIZEM CD is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

CARDIZEM CD is indicated for the management of chronic stable angina and angina due to coronary artery spasm.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General

CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with other agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers. Controlled and uncontrolled domestic studies sugest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis. Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy

Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater. There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

[See table top left of next page.]

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

Continued on next page

Marion Merrell Dow—Cont.

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined

Adverse Reaction	Cardizem CD N=607	Placebo N=301
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermitits, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocyloclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases.

There have been 29 reports of diltiazem overdose in doses ranging from less than 1 gm to 10.8 gm. Sixteen of these reports involved multiple drug ingestions.

Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 gm to 10.8 gm. There were seven reports with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure, inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered:

Bradycardia: Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously

High-degree AV Block: Treat as for bradydcardia above. Fixed high-degree AV block should be treated with cardiac pacing

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics

Hypotension: Vasopressors (eg, dopamine or levarterenol bitartrate)

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION

Patients controlled on diltiazem alone or in combination with other medications may be safely switched to CARDIZEM CD capsules at the nearest equivalent total daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. There is limited general clinical experience with doses above 360 mg, but doses to 540 mg have been studied in clinical trials. The incidence of side effects increases as the dose increases with first-degree AV block, dizziness and sinus bradycardia bearing the strongest relationship to dose.

Hypotension. Dosage needs to be adjusted by titration to individual patient needs. When used as monotherapy, reasonable starting doses are 180 to 240 mg once daily, although some patients may respond to lower doses. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy, therefore, dosage adjustments should be scheduled accordingly. The usual dosage range studied in clinical trials was 240 to 360 mg once daily. Individual patients may respond to higher doses of up to 480 mg once daily.

Angina. Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 or 180 mg once daily. Individual patients may respond to higher doses of up to 480 mg once daily. When necessary, titration may be carried out over a 7 to 14 day period.

Concomitant Use With Other Cardiovascular Agents

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM CD (diltiazem hydrochloride) therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM CD may be safely coadministered with short- and long-acting nitrates.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS)
4. **Antihypertensives**—CARDIZEM CD has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of CARDIZEM CD or the concomitant antihypertensives may need to be adjusted when adding one to the other.

HOW SUPPLIED

[See table below.]

Storage Conditions: Store at controlled room temperature 59–86° F (15–30° C)

Avoid excessive humidity.

Prescribing information as of October 1992 (2)

Marion Merrell Dow Inc.
Kansas City, MO 64114

Shown in Product Identification Section, page 316

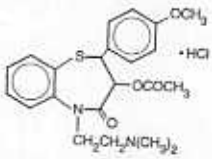
CARDIZEM CD
(diltiazem hydrochloride)
Capsules

Strength	Quantity	NDC Number	Description
120 mg	30 btl 90 btl 100 UDIP®	0088-1795-30 0088-1795-42 0088-1795-49	Light turquoise blue/light turquoise blue capsule imprinted with the Marion Merrell Dow Inc. logo on one end and CARDIZEM CD and 120 mg on the other.
180 mg	30 btl 90 btl 100 UDIP®	0088-1796-30 0088-1796-42 0088-1796-49	Light turquoise blue/blue capsule imprinted with the Marion Merrell Dow Inc. logo on one end and CARDIZEM CD and 180 mg on the other.
240 mg	30 btl 90 btl 100 UDIP®	0088-1797-30 0088-1797-42 0088-1797-49	Blue/blue capsule imprinted with the Marion Merrell Dow Inc. logo on one end and CARDIZEM CD and 240 mg on the other.
300 mg	30 btl 90 btl 100 UDIP®	0088-1798-30 0088-1798-42 0088-1798-49	Light gray/blue capsule imprinted with the Marion Merrell Dow Inc. logo on one end and CARDIZEM CD and 300 mg on the other.

CARDIZEM® Injectable
(diltiazem hydrochloride)

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-benzothiazepin-4(5H)one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98.

CARDIZEM Injectable (diltiazem hydrochloride) is a clear, colorless, sterile, nonpyrogenic solution. It has a pH range of 3.7 to 4.1.

CARDIZEM Injectable is for direct intravenous bolus injection and continuous intravenous infusion.

25-mg, 5-mL vial—each sterile vial contains 25 mg diltiazem hydrochloride, 3.75 mg citric acid USP, 3.25 mg sodium citrate dihydrate USP, 357 mg sorbitol solution USP, and water for injection USP up to 5 mL. Sodium hydroxide or hydrochloric acid is used for pH adjustment.

50-mg, 10-mL vial—each sterile vial contains 50 mg diltiazem hydrochloride, 7.5 mg citric acid USP, 6.5 mg sodium citrate dihydrate USP, 714 mg sorbitol solution USP, and water for injection USP up to 10 mL. Sodium hydroxide or hydrochloric acid is used for pH adjustment.

CLINICAL PHARMACOLOGY

Mechanisms of Action. CARDIZEM inhibits the influx of calcium (Ca^{2+}) ions during membrane depolarization of cardiac and vascular smooth muscle. The therapeutic benefits of CARDIZEM in supraventricular tachycardias are related to its ability to slow AV nodal conduction time and prolong AV nodal refractoriness. CARDIZEM exhibits frequency-dependent effects on AV nodal conduction such that it may selectively reduce the heart rate during tachycardias involving the AV node with little or no effect on normal AV nodal conduction at normal heart rates.

CARDIZEM slows the ventricular rate in patients with a rapid ventricular response during atrial fibrillation or atrial flutter. CARDIZEM converts paroxysmal supraventricular tachycardia (PSVT) to normal sinus rhythm by interrupting the reentry circuit in AV nodal reentrant tachycardias and reciprocating tachycardias, eg, Wolff-Parkinson-White syndrome (WPW).

CARDIZEM prolongs the sinus cycle length. It has no effect on the sinus node recovery time or on the sinoatrial conduction time in patients without SA nodal dysfunction.

CARDIZEM has no significant electrophysiologic effect on tissues in the heart that are fast sodium channel dependent, eg, His-Purkinje tissue, atrial and ventricular muscle, and extranodal accessory pathways.

EXHIBIT K

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Comparison of diltiazem bioavailability from 3 marketed extended-release products for once-daily administration: implications of chronopharmacokinetics and dynamics

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Abstract. Diltiazem has proven to be an effective antihypertensive and antianginal agent, due to its potent calcium channel blocking activity. The present study was conducted to compare the bioavailability of a new extended release diltiazem HCl capsule formulation (Tiazac) with 2 other currently marketed products (Cardizem CD and Dilacor XR). Fourteen healthy male subjects participated in this randomized, 3-period, multiple daily dose (240 mg for 7 days), crossover bioavailability study. ANOVA and multiple comparison tests showed the parent drug $AUC_{0-\tau}$ to be significantly higher after daily dosing with Tiazac than with the other 2 marketed products, but the diltiazem C_{min} values were not significantly different between the 3 formulations. Between 5 and 12 hours after drug administration, mean plasma diltiazem levels for Tiazac capsules were found to be significantly higher than those of the 2 other products tested. Comparison of plasma concentrations of metabolites for the 3 capsule formulations by ANOVA and multiple comparison tests showed similar trends as in the case of parent drug concentrations. These findings may be clinically important as higher and more consistent plasma concentrations of diltiazem, and its active metabolite during daytime are needed to counteract higher blood pressures in hypertensive patients due to circadian variations. The new extended release product of diltiazem HCl was found to exhibit significantly differing pharmacokinetics of the parent compound compared to either of the other 2 products tested.

Key words: bioavailability – diltiazem – clinical significance – controlled release – pharmacokinetics

Introduction

Diltiazem is a potent calcium channel blocker and its role in the management of essential hypertension is well established [Oates 1996]. While the drug is readily absorbed, it exhibits low bioavailability and short half-life due to substantial first-pass metabolism [Herman et al. 1983]. On account of these pharmacokinetic properties, all immediate release diltiazem HCl products are considered short-acting because patients generally have to ingest them 3 – 4 times a day to effect adequate blood pressure control. Twice-and once-a-day extended release diltiazem formulations have been available for several years. A major advantage of extended release formulations of the drug is optimization of antihypertensive therapy by improving patient compliance and safety, the latter through elimination of multiple peaks in plasma diltiazem concentrations due to 3- to 4-times-a-day-dosing of immediate release formulations. Tiazac is a new extended release capsule formulation of diltiazem hydrochloride for once-a-day dosing, which recently became available in the United States and Canada. This study was conducted during the clinical development of Tiazac capsules to compare its pharmacokinetic profile with those of 2 other FDA-approved drug products, Cardizem CD and Dilacor XR, capsules. In this report, comparison of pharmacokinetic profiles of 3 drug products and their clinical implications are discussed.

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Methods, materials, and subjects

The protocol was approved by the Institutional Review Board of the Contract Research Organization where the study was conducted. Fourteen healthy male volunteers

with ages ranging from 21 – 37 years and weighing 55 – 95 kg were admitted into the study. Written informed consents were obtained from the volunteers. The new formulation (240 mg Tiazac capsules-marketed in Canada and the USA by Crystaal Corporation and Forest Labs Inc., respectively-, Biovail Corporation International), is a multiparticulate system consisting of polymer-coated beads in hard gelatin capsules. The 2 other formulations were 240 mg Cardizem CD capsules (Marion Laboratories) and 240 mg Dilacor XR capsules (Rhone-Poulenc Rorer). Each of these 3 formulations was administered once daily over a 7-day study period in a crossover design. Each subject received all 3 formulations; the formulation sequences for individual subjects were assigned according to a randomization schedule. There was a 1-week washout period between drug administrations.

In each period subjects were institutionalized in the clinic the evening prior to drug administration. They fasted from 10 p.m. the evening prior to dosing until specified meal times. Dosing was at 7 a.m. daily and the subjects ingested the assigned formulation with 240 ml of water. On days 1 through 6 of each dosing period, standardized, caffeine-free meals were ingested by the subjects at 9:30 a.m., 1 p.m., 6 p.m., and 10 p.m. On day 7 of each study period, meals were provided at 11:30 a.m., 4:30 p.m., and 10 p.m. Vital signs and ECGs were monitored at predetermined times throughout the study.

On day 1, and days 4 through 7, a pre-dose blood sample (10 ml each) was collected at 7 a.m. Post-dose steady-state blood samples (10 ml each) on day 7 were collected at 1, 2, 3, 4, 5 6, 7, 8, 10, 12, 16, 20, and 24 hours. Precooled EDTA vacutainers were used for blood sample collection. All blood samples were centrifuged within 15 minutes of collection and the plasma portions were harvested, frozen, and stored at –70° C until analysis. A validated HPLC procedure [Eradiri and Midha 1995] was used in the analysis of the plasma samples for levels of diltiazem (DTZ) and its 2 major metabolites, desacetyldiltiazem (DEA) and N-desmethyldiltiazem (DEM). The calibration ranges for DTZ, DEA, and DEM were 3 – 800, 1 – 200, and 3 – 700 ng/ml, respectively. Interday coefficients of variation for the lower limits of quantitation were 9.5%, 8%, and 10.4% for DTZ, DEA, and DEM, respectively. Intra- and interassay precisions of the method were less than 5% for all 3 analytes.

The areas under the plasma concentration versus time curves ($AUC_{0-\tau}$) were calculated using the linear trapezoidal method. The maximum analyte plasma concentrations (C_{max}), minimum plasma concentrations (C_{min}) and the time to attain C_{max} (t_{max}) were taken directly from the raw data. The degree of fluctuation was calculated using the formula: $100 \times ((C_{max} - C_{min})/(AUC_{0-\tau/24}))$. The predose plasma concentrations for all 3 analytes on days 4 through 7 were tested for differences (ANOVA) to determine if steady-state was attained. ANOVAs were also performed on plasma concentrations for all 3 analytes at protocol-specified sampling time points to determine formulation differences, if any. The pharmacokinetic parameters of Tiazac were compared with those of the 2 formulations tested for all 3 analytes by ANOVA at the 5% level of significance using SAS General Linear Model Procedure. Geometric 90% confidence intervals calculated using the two 1-sided test procedure [Schuirmann 1987] were determined for $AUC_{0-\tau}$, C_{max}, and C_{min} ratios between the new formulation and each of the 2 other formulations. Confidence intervals for ratios falling outside 0.80 – 1.25 were deemed bioinequivalent. In cases, where ANOVA detected significant differences, the Duncan's multiple comparison test was performed.

Results

All 14 subjects completed the study in its entirety. ANOVA of each product's predose C_{min} values on days 4 through 7 for all 3 analytes (DTZ, DEA, and DEM) did not reveal any differences; this outcome indicated steady-state was achieved in each case.

The mean steady-state plasma DTZ, DEA, and DEM concentration versus time curves on day 7 for all 3 extended release formulations are presented in Figure 1. Plasma diltiazem concentrations for all 3 formulations gradually increased after morning dosing to peak concentrations which occurred between 5 and 7 hours, upon reaching C_{max}, higher levels of plasma diltiazem were maintained longer after Tiazac relative to Cardizem CD and Dilacor XR. In addition, Tiazac consistently provided significantly higher plasma diltiazem concentrations from hour 5 to hour 12 when compared to either of the other 2 products (Table 1). There were no statistically significant differences among the plasma diltiazem concentrations exhibited by the 3 formulations between 20 and 24 h post dose. Plasma concentration versus time curves for the 2 metabolites showed similar trends. The plasma DEA concentrations following Tiazac administration were significantly higher than those of Cardizem CD and Dilacor XR at 6, 7, 8, 9, 10, and 12 h. In the case of DEM, significantly higher plasma levels due to Tiazac capsules were observed at 5, 6, 7, and 12 h.

Table 2 presents a summary of the means of pertinent pharmacokinetic parameters for the 3 formulations. For the parent drug, Tiazac demonstrated significantly higher $AUC_{0-\tau}$ (> 20%) than either of the 2 other marketed products. While the steady-state diltiazem C_{min} values for all 3 formulations were not different, Tiazac had a significantly higher (> 20% higher) diltiazem C_{max} value than either of the 2 other formulations tested. All 3 products exhibited similar degree of fluctuation of diltiazem plasma concentrations. The metabolites' pharmacokinetic parameters showed that Tiazac exhibited significantly greater mean DEA and DEM $AUC_{0-\tau}$ values than the other 2 formulations. While the DEA and DEM C_{max} values for Tiazac

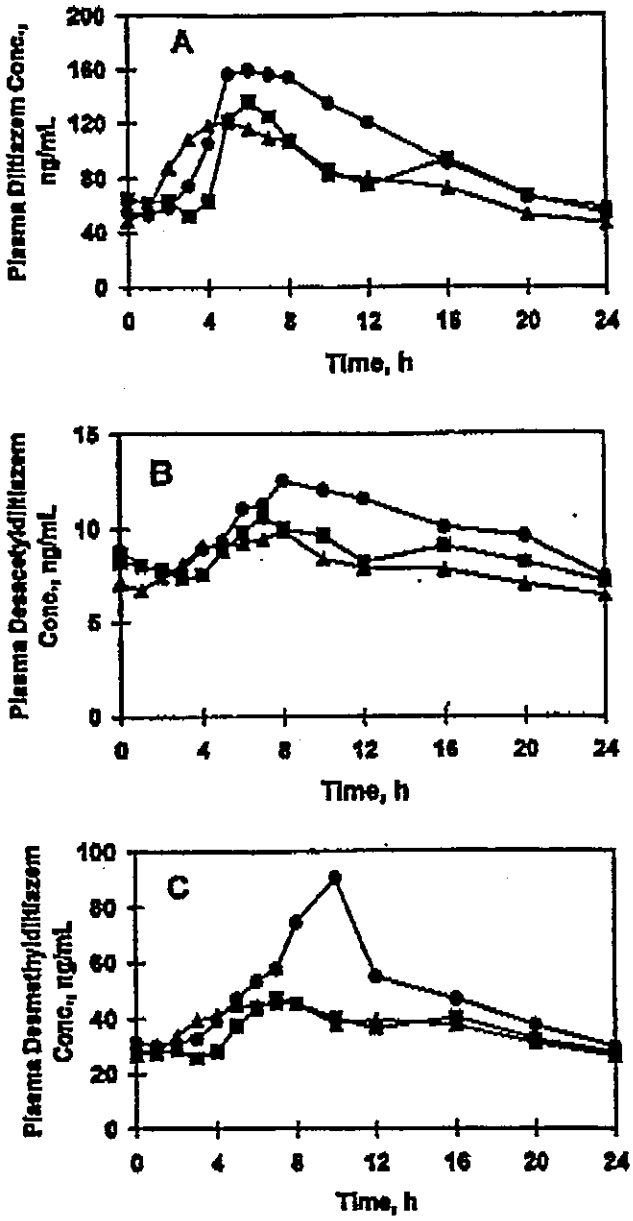

Fig. 1 Mean diltiazem (A), desacetyldiltiazem (B), N-desmethyldiltiazem (C) plasma concentration versus time curves on day 7 after daily doses of 3 different brands of 240 mg diltiazem extended-release formulation (Tiazac ●, Cardizem CD ■, and Dilacor XR (▲) in 14 healthy male volunteers. (Tiazac is marketed in Canada and the United States by Crystaal Corporation and Forest Labs Inc., respectively.)

were significantly higher than the corresponding C_{max} values for the 2 other formulations, the C_{min} values of both primary metabolites were not different for the 3 formulations.

The point estimates of key bioequivalence parameters of Tiazac (the test formulation) to those of the 2 other formulations (as references) are also presented in Table 2 for all 3 analytes. The 90% geometric confidence intervals

Table 1 Steady-state (mean ± SE) plasma diltiazem concentrations following daily administration of 240 mg diltiazem HCl for 7 days as 3 different extended release capsules to 14 healthy male volunteers.

Sampling time (h)	Tiazac	Cardizem CD	Dilacor XR	p value
0	55.1 ± 5.4	65.0 ± 8.4	48.3 ± 5.3	n.s.
	53.0 ± 5.8	61.7 ± 9.1	57.2 ± 6.7	n.s.
2*	58.7 ± 5.7^b	63.5 ± 8.3^b	87.9 ± 9.0^a	0.003
3*	74.1 ± 7.2^b	52.4 ± 6.4^c	108.6 ± 10.2^a	0.0001
4*	105.8 ± 11.5^a	62.8 ± 5.1^b	118.6 ± 9.7^a	0.0001
5*	156.9 ± 15.5^a	122.8 ± 14.6^b	121.0 ± 14.2^b	0.0382
6*	160.1 ± 11.5^a	136.4 ± 11.1^b	115.9 ± 11.1^c	0.0002
7*	156.8 ± 10.4^a	125.7 ± 11.8^b	109.5 ± 11.3^b	0.0009
8*	154.5 ± 9.1^a	107.5 ± 9.9^b	107.0 ± 11.6^b	0.0001
10*	135.7 ± 9.1^a	86.3 ± 7.2^b	82.4 ± 8.0^b	0.0001
12*	120.8 ± 9.2^a	74.6 ± 7.2^b	79.8 ± 7.3^b	0.0001
16*	90.7 ± 7.4^a	93.7 ± 9.2^a	72.1 ± 8.4^b	0.0234
20	65.6 ± 5.8	66.7 ± 6.2	52.9 ± 5.3	n.s.
24	58.2 ± 8.0	53.8 ± 5.3	46.7 ± 4.3	n.s.

* = $p < 0.05$ treatment means with different letters were significantly different (ANOVA followed by multiple comparison test)

for the parent drug and metabolites' $AUC_{0-\tau}$ comparisons consistently had statistical power > 0.80. Tiazac exhibited mean diltiazem $AUC_{0-\tau}$ which was 24% and 29% greater than the corresponding mean diltiazem $AUC_{0-\tau}$ values for Cardizem CD and Dilacor XR, respectively. The mean $AUC_{0-\tau}$'s of DEA and DEM for Tiazac were 18 – 29% greater than the corresponding values for the other 2 marketed products used in this study as references.

Discussion

Tiazac, the new extended release diltiazem HCl product for once daily administration, was found to provide 24 and 29% greater parent drug exposure in the present steady-state study than Cardizem CD or Dilacor XR, respectively. The outcomes with respect to the primary metabolites' AUC comparisons were similar to those of the parent drug. Tiazac is therefore bioinequivalent to either Cardizem CD or Dilacor XR. The analyses of peak exposure, i.e. C_{max} values and plasma drug levels, at individual sampling time points showed that the greater bioavailability with Tiazac could be attributed to higher concentrations of diltiazem and metabolites from hour 5 through hour 12 after daily dosing with the new extended release formulation.

Clinically it is of interest to examine the significance of the observed differences in bioavailability of diltiazem from the 3 extended release products. It is noted that the shapes of the plasma concentration versus time profiles for diltiazem and its 2 primary metabolites after dosing of the new extended release formulation (Tiazac capsules) were markedly different from those of Cardizem CD and Dilacor XR (Figure 1). The plasma desacetyldiltiazem and N-des-

Table 2 Steady-state pharmacokinetic parameters of DTZ, DEA, and DEM following daily administration of 240 mg diltiazem hcl for 7 days as 3 different extended-release capsules to 14 healthy male volunteers.

Analyte	PK parameters	Formulation	Mean	Test/Ref Ratio‡, %
Diltiazem	AUC_{0-t}*† (ng×hr/ml)	Tiazac	2,345 (1413 – 3570)[a]	
		Cardizem CD	1,882 (1,128 – 3,174)[b]	124 (110 – 139)
		Dilacor XR	1,808 (1032 – 3417)[b]	129 (115 – 145)
	C_{max}*† (ng/ml)	Tiazac	178 (124 – 305)[a]	
		Cardizem CD	147 (98 – 218)[b]	121 (106 – 138)
		Dilacor XR	125 (79 – 222)[b]	142 (125 – 162)
	C_{min}† (ng/ml)	Tiazac	44 (25 – 75)	
		Cardizem CD	42 (22 – 86)	106 (86 – 131)
		Dilacor XR	40 (15 – 84)	110 (90 – 135)
	t_{max}* (hours)	Tiazac	7.0 ± 1.8[a]	
		Cardizem CD	5.4 ± 1.5[b]	
		Dilacor XR	5.4 ± 2.0[b]	
	Degree of fluctuation (%)	Tiazac	139 ± 36	
		Cardizem CD	134 ± 40	
		Dilacor XR	114 ± 38	
Desacetyldiltiazem**	AUC_{0-t}*† (ng hr/ml)	Tiazac	230 (152 – 427)[a]	
		Cardizem CD	196 (104 – 366)[b]	118 (107 – 131)
		Dilacor XR	179 (99 – 363)[b]	129 (117 – 143)
	C_{max}*† (ng/ml)	Tiazac	13.1 (9.4 – 21.9)[a]	
		Cardizem CD	10.7 (5.9 – 18.7)[b]	122 (108 – 137)
		Dilacor XR	10.1 (5.3 – 18.4)[b]	130 (115 – 146)
	C_{min}† (ng/ml)	Tiazac	6.4 (3.2 – 12.1)	
		Cardizem CD	5.9 (2.4 – 11.8)	108 (91 – 127)
		Dilacor XR	5.3 (3.2 – 11.4)	119 (100 – 141)
	t_{max} (hours)	Tiazac	8.6 ± 2.0	
		Cardizem CD	10.2 ± 4.6	
		Dilacor XR	7.4 ± 2.8	
N-Desmethyldiltiazem	AUC_{0-t}*† ng hr/ml)	Tiazac	1,064 (651 – 1,509)[a]	
		Cardizem CD	846 (605 – 1,143)[b]	125 (113 – 139)
		Dilacor XR	854 (477 – 1,314)[b]	129 (112 – 138)
	C_{max}*† (ng/ml)	Tiazac	74 (50 – 509)[a]	
		Cardizem CD	48 (31 – 68)[b]	151 (117 – 195)
		Dilacor XR	47 (26 – 81)[b]	154 (119 – 199)
	C_{min}† (ng/ml)	Tiazac	28 (17 – 40)	
		Cardizem CD	24 (14 – 39)	118 (102 – 136)
		Dilacor XR	24 (14 – 38)	118 (102 – 135)
	t_{max} (hours)	Tiazac	8.5 ± 2.1	
		Cardizem CD	7.9 ± 2.7	
		Dilacor XR	6.8 ± 3.4	

†= geometric means, numbers in parentheses are ranges, * = $p < 0.05$ treatment means with different letters were significantly different, ‡ numbers in parentheses are 90% geometric confidence intervals, t_{max} and degree of fluctuation are expressed as mean ± SD, ** n = 13

methyldiltiazem levels in the present study were approximately 10 and 40%, respectively, of the parent drug concentrations. To date, the role of these 2 metabolites in antihypertensive therapy has not been well established. While desacetyldiltiazem is 25 – 50% as active as the parent drug as a vasodilator, there is little information on the potency of N-desmethyldiltiazem. Nevertheless, the fact that Tiazac delivered sustained and greater plasma concentrations of the parent drug from hour 5 to hour 12 after dosing as compared to the other marketed once daily products, may be an important finding from a chronotherapeutic perspective.

Circadian fluctuations in the onset of acute cardiovascular disease have prompted researchers to examine the diurnal cycles of heart rate and blood pressures [Muller and Willich 1996]. Heart rate exhibits a sharp rise in the morning and stays elevated throughout the day; heart rate slows down substantially at night. There is an early morning rise

in heart rate at around 4 a.m. Blood pressure follows a similar pattern. Highest blood pressures are observed between 9 a.m. and late afternoon. The daytime blood pressures are 20 – 30 mmHg higher than the nighttime blood pressures. Hence, from a chronotherapeutic perspective, an extended release antihypertensive product which can deliver sustained high plasma drug levels throughout the day may be especially advantageous to patients during the day. Tiazac possesses a plasma diltiazem concentration versus time profile which is appealing and suited for chronotherapeutic aspects of hypertension. This observation has support from a pharmacokinetic-pharmacodynamic consideration. In a recent clinical efficacy study with this new extended release product [Lacourciere et al. 1995], increasing the dose of Tiazac was associated with proportional reduction in blood pressure ($r = 0.99$). Hence, it is reasonable to postulate that higher steady-state plasma diltiazem concentrations are likely to result in greater antihypertensive effect during the day when clinical benefit is most needed.

Diastolic and systolic blood pressures, heart rate, and PR intervals were measured at predetermined times in each phase of this study for safety reasons only. Since it is well known that diltiazem does not elicit significant pharmacodynamic responses in healthy volunteers [Guimont et al. 1993], the study was not designed to evaluate differences in hemodynamics between the drug products. The relationship between plasma diltiazem levels and pharmacodynamic effects are better investigated in a controlled clinical trial using hypertensive patients.

Conclusion

Tiazac, a new once-a-day extended release capsule formulation of diltiazem HCl, exhibited greater diltiazem bioavailability than either of the other 2 extended release formulations marketed for once daily dosing. The increase in diltiazem bioavailability with Tiazac was due to sustained higher plasma concentrations from hour 5 to hour 12 after dosing. From a chronotherapeutic perspective, this new once-a-day capsule formulation may offer an advantage over other such diltiazem products in the treatment of hypertension.

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